

Brief Title: GER Poses a Potential Risk for Late Complications of BPD

Official Title: Gastroesophageal Reflux Really Pose a Potential Risk for Late Complications of Bronchopulmonary Dysplasia in Extremely Premature Infants

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Sponsor: Shengjing Hospital

Investigator: Shucheng Zhang

Official Title: Professor

Affiliation: Shengjing Hospital

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Study Protocol

Research background

Bronchopulmonary dysplasia (BPD) is a common condition in the low birth weight infants. Although most of the BPD symptoms improved after a regular treatment in infancy, there are still a few late complications left such as the frequent respiratory symptoms, a slower weight gain and even sudden death. These late complications have made so much trouble to the healthcare of BPD infants. How to find the risk factors and to reduce the prevalence of these late symptoms becomes necessary. In this study, a cohort of BPD infants was observed with the late complications obtained by a monthly followed up for 18 months after discharge, the prevalence and risk factors were analyzed via logistic regression, calculating odd ratios (OR) and 95% confidence intervals. As one of the risk factors, GER was verified whether to play a critical role in these late complications.

Research purposes

A prospective cohort study is carried out to explore the potential risk of gastroesophageal reflux as a late complication of bronchopulmonary dysplasia in preterm infants.

Methods

Patients

The study was approved by the Ethics Committee of China Medical University. Written consent was obtained from the parents. The cohort included infants born at or before 32 weeks gestational age (GA) with BPD between January 2017 and July 2018 at Shengjing Hospital of China Medical University, the First Hospital of Jilin University, and Shanghai General Hospital of Shanghai Jiao Tong University. BPD was diagnosed at 36 weeks postmenstrual age (PMA) on the National Heart, Lung and Blood Institute classification and categorized as “mild, moderate or severe”. Infants with no BPD, severe gastrointestinal malformations and refused GER monitoring were excluded.

Detailed information on the BPD infants, including age, sex, Apgar scores, treatments after

born, clinical symptoms, and other clinical information we designed. After discharge, all the patients received a regular follow up for late complications including respiratory symptoms (including home respiratory support, respiratory medication administration, cough without cold at least once per week, re-hospitalization due to respiratory diseases), vomiting when feeding, hypoxic ischemic injury, retinopathy of prematurity, rehospitalization and sudden death.

Measurements and definitions

Respiratory morbidity included pneumonia, respiratory medication administration for dyspnea, cyanosis and intermittent apnea, and cough without cold at least once per week. Vomiting when feeding referred to vomiting at least once a week and retinopathy of prematurity were diagnosed by local doctors. The diagnoses of hypoxic-ischemic injury mainly depend on MRI.

pH-MII methods

A 24h pH-MII measurement was carried out twice in each infant in the study group of 116 infants with BPD. The first test was performed at 36 weeks PMA and the second, at the last interview between the 17th and 18th month of PMA. Pathological GER was diagnosed when both the tests were positive for GER. In pH-MII monitoring, the probe (Kanglian, Beijing, China) had eight impedance channels (Z1-Z6) and two pH channels. The probe was inserted transnasally into the esophagus. The proximal pH channel was positioned 3 cm above the left diaphragm and the distal pH channel was positioned in the stomach. The position of the pH channels was verified by chest radiography. The data were evaluated using the manufacturer's software and each trace was manually reviewed by the same operator. This operator was not informed of the final outcome.

GER was diagnosed based on the proximal pH channel. Reflux index (RI), which is the percentage of the total recording time with an esophageal pH < 4, was used to categorize pathological GER. Acid GER was defined by a RI > 12, irrespective of the impedance value. Weak acid reflux was defined as a pH between 4–7 when the impedance value decreased > 20% from the baseline while the duration of intragastric pH > 4 for < 70% of the time. DGER was diagnosed for RI < 12 with decreasing impedance and when the intragastric pH > 4 for > 70% of the time. GER without acid GER and DGER was regarded as non GER.

Determination of gastric sodium ions

The gastric juice was sampled from 89 infants. All medications were forbidden 24 hours prior to sample collection. A feeding tube was always placed for daily meals. Gastric juice was taken for 30 minutes via the feeding tube before meal at 2AM, 10AM and 6PM in a given day with an interval of 8 hours, and was analyzed on a rapid ion analyzer (BHF-II, Bairikang, Beijing). Each patient was sampled three times and a Na⁺ concentration > 50 mmol/L in all three samples was considered positive.

Statistics

Continuous variables were graded as categorical variables and the categorical variables were expressed as frequency and percentage. Chi-square test was used to compare categorical differences. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for every late complication of BPD were estimated separately with multiple logistic regression models (forward). Potential confounders included gender, GA (< 30 weeks and ≥ 30 weeks), birth weight (< 1500 g and > 1500 g), Apgar score, invasive ventilation (< 7 days and ≥ 7 days), pulmonary surfactant, caffeine, ventilator-associated pneumonia, and GER were

adjusted. All computations relied on standard software (SPSS v19.0; SPSS Inc, Chicago, IL, USA), and statistical significance was set at $P < 0.05$.

Results

Prevalence of Late Complications

Among the 116 infants with BPD in the final cohort, late complications occurred in 74 infants with an overall prevalence of 63.79%. These complications included respiratory symptoms in 49.14% (n=57) infants, including pneumonia (n=10, 8.62%); dyspnea, cyanosis and intermittent apnea warranting respiratory medication administration (n=25, 21.55%), and cough (n=44, 37.93%). Vomiting occurred in 45 (38.79%), ROP in 30 (25.86%), and hypoxic-ischemic injury in 4 (3.45%) infants. One (0.86%) infant suffered sudden infant death syndrome. Re-hospitalization was recorded in 31 (26.72%) infants.

GER Prevalence in BPD

Pathological GER occurred in 49 infants with BPD with an overall prevalence of 42.24%, including acid GER (n=21, 18.10%) and DGER (n=28, 24.14%). SI, SSI, and SAP measurements were $> 99\%$ in all 49 infants, confirming the association between reflux events and symptoms. Weak acid GER was found in almost all infants including those with acid GER, DGER and non GER. The percentage of weak acid GER events over the overall reflux episodes varied from 40.74–100%, and there was no significant difference among infants with acid GER, DGER and non GER. In the evaluation of DGER, 33 infants are positive for pH-MII monitoring, and gastric $\text{Na}^+ > 50 \text{ mmol/L}$ was noted in 28 infants who were finally diagnosed as DGER. Five infants positive for pH-MII and negative for gastric $\text{Na}^+ > 50 \text{ mmol/L}$ were diagnosed as weak acid GER. No infants negative for pH-MII and positive for

gastric $\text{Na}^+ > 50 \text{ mmol/L}$ were noted. Among the BPD infants, the prevalence of acid GER and DGER was 12% and 17.33% in mild BPD, 32.14% and 32.14% in moderate BPD, and 23.08% and 46.15% in severe BPD individually. Among the 74 symptomatic infants, the prevalence was 14.66% and 21.55%.

Risk Factors for Late Complications

Accordingly, risk factors for respiratory symptoms were $\text{GA} \leq 30$ weeks (odds ratio, $\text{OR}=3.213$; 95% CI, 1.221-8.460), birth weight $< 1500 \text{ g}$ ($\text{OR}=2.803$; 95% CI, 1.014-7.749), invasive ventilation > 7 days ($\text{OR}=4.952$; 95% CI, 1.508-16.267), acid GER ($\text{OR}=4.630$; 95% CI, 1.305-16.420), and DGER ($\text{OR}=5.588$; 95% CI, 1.770-17.648). Risk factors for vomiting were $\text{GA} \leq 30$ weeks ($\text{OR}=5.813$; 95% CI, 2.424-13.940), acid GER ($\text{OR}=3.394$; 95% CI, 1.107-10.403), and DGER ($\text{OR}=4.379$; 95% CI, 1.552-12.354). Risk factors for ROP were $\text{GA} \leq 30$ weeks ($\text{OR}=8.741$; 95% CI, 3.203-23.851), while the major risk factors for re-hospitalization were $\text{GA} \leq 30$ weeks ($\text{OR}=3.894$; 95% CI, 1.405-10.791), acid GER ($\text{OR}=5.866$; 95% CI, 1.640-20.972), and DGER ($\text{OR}=8.436$; 95% CI, 2.697-26.382).

Conclusion

In summary, the prevalence of late complications of BPD is high; pediatricians should pay great attention to BPD infants after discharge to reduce the damage caused by these late complications. GER, or rather DGER, is a potential risk for the late complications of BPD.